REMARKS

Reconsideration of the present application is respectfully requested in view of the above amendments and the following remarks. Claims 1, 17, and 44-45 are currently pending and under examination. Without acquiescence or prejudice, claim 1 is amended to particularly point out and distinctly claim certain embodiments of Applicants' invention. No new matter has been added by the amendments. Support for the amendments can be found in the specification as filed, for example, at page 1, lines 22-25; page 5, lines 27-23; page 14, lines 13-27, and elsewhere.

Rejections Under 35 U.S.C. § 112, First Paragraph, Written Description

The Examiner rejected claims 1, 17, and 44-45 under 35 U.S.C. § 112, first paragraph, for alleged lack of written description. The Examiner asserts that the recitation "wherein the receptor protein is non-glycosylated" represents new matter.

Applicants traverse this rejection and submit that the instant claims satisfy the written description requirement. Nonetheless, without acquiescence, the recitation "wherein the receptor protein is non-glycosylated" is deleted from claim 1, and is replaced with "wherein the receptor is an extracellular region or C-type lectin-like domain (CTLD) of a scavenger receptor LOX-1" (*see, e.g.,* page 1, lines 22-25 of the specification for support). Applicants believe that this amendment renders the rejection moot.

Applicants submit that the instant claims as amended herewith satisfy the written description requirement under 35 U.S.C. § 112, first paragraph, and kindly request withdrawal of this rejection.

Rejections Under 35 U.S.C. § 103

A. The Examiner has maintained the rejection of claim 1 under 35 U.S.C. 103(a) as being allegedly obvious over Holtzman (U.S. Patent No. 5,969,123) in view of Schatz (U.S. Patent No. 5,932,433) and further in view of Tall *et al.* (U.S. Patent No. 6,756,228). The Examiner asserts that Holtzman teaches a biochip comprising a biotinylated receptor protein immobilized via a biotinylation sequence motif, wherein the receptor protein has the ability of

being specifically bound by a ligand of the receptor protein. The Examiner also asserts that Schatz teaches a recombinantly expressed biotinylated receptor protein immobilized via a factor capable of specifically binding to biotin. The Examiner further asserts that Tall *et al.* teach a non-glycosylated LOX-1 receptor immobilized to a substrate in order to detect the presence of LOX-1 activity. The Examiner then asserts that it would have been obvious to perform biotinylation of the receptor protein as described in Holtzman *in vivo* instead of *in vitro* as taught by Schatz to provide a simplified biotinylation process, and that it would have been further obvious to include as the receptor protein of Holtzman in view of Schatz, a receptor protein of LOX-1 as taught by Tall *et al.*

B. The Examiner has maintained the rejection of claims 17 and 44 under 35 U.S.C. 103(a) as being allegedly obvious over Brigham-Burke *et al.* (U.S. Patent No. 5,395,587) in view of Holtzman and further in view of Schatz and Tall *et al.* The Examiner relies on Holtzman, Schatz and Tall *et al.*, as discussed in section A above, and further asserts that Brigham-Burke *et al.* teach a protein immobilized on a sensor chip substrate that conforms to a shape of an insertion site of a surface plasmon resonance device, which allegedly renders the instant claims obvious.

C. The Examiner has also maintained the rejection of claims 17 and 45 under 35 U.S.C. 103(a) as being obvious over Muramatsu (*Analytical Chemistry*, 1987;59:2760-2763) in view of Holtzman, and further in view of Schatz and Tall *et al.* The Examiner relies on Holtzman, Schatz and Tall *et al.*, as discussed in section A above, and further asserts that Muramatsu teaches a protein immobilized on a crystal oscillator, which allegedly renders the instant claims obvious.

Applicants traverse these rejections and submit that the instant claims satisfy the requirements of non-obviousness. Applicants submit that the Examiner has failed to establish a *prima facie* case of obviousness over these claims. *See In re Mayne*, 104 F.3d 1339 (Fed. Cir. 1997) (The USPTO has the burden of showing a *prima facie* case of obviousness). Mainly, it is respectfully submitted that the cited references (i) fail to ***teach or suggest each feature of the instant claims***, and (ii) fail to provide any motivation to practice the presently claimed subject matter with a ***reasonable expectation of success***. *See KSR v. Teleflex, Inc.,* No. 04-1350 at 4, 14

(U.S. Apr. 30, 2007) ("A patent composed of several elements is not proved obvious merely by demonstrating that each element was, independently, known in the prior art").

The cited references ***in combination*** fail to teach or suggest each feature of the instant claims. For instance, none of Holtzman, Schatz or Tall *et al.* teach or suggest a functional extracellular region or a C-type lectin-like domain (CTLD) of a LOX-1 receptor that is obtained by refolding the ***biotinylated protein*** expressed as an ***inclusion body*** within the bacterial host, as recited in the instant claims. Indeed, none of the cited references teach refolding a biotinylated protein expressed as ***inclusion bodies***. Given that appropriate refolding from inclusion bodies is required to obtain a functional receptor chip that binds its endogenous ligand, the instant feature relates to more than just a step (*see* the Action, page 5), but rather reflects the inherent structural features of a recombinantly produced, properly refolded extracellular region or CTLD of a LOX-1 protein. The cited references in combination fail to teach or suggest a recombinant protein having these inherent structural features, and, therefore, fail to provide the requisite elements of a *prima facie* case of obviousness.

Even assuming, *arguendo*, that the cited references teach or suggest each feature of the instant claims, these references fail to motivate persons skilled in the art to practice the presently claimed subject matter with a ***reasonable expectation of success***. Applicants submit that a reasonable expectation of success is a ***required*** element of a *prima facie* case of obviousness, which ***must*** be established by technical reasoning or evidence or both. *See, e.g., See KSR v. Teleflex, Inc.* at 14, citing *In re Kahn,* 441 F.3d 977, 988 (Fed. Cir. 2006) ("[R]ejections on obviousness grounds cannot be sustained by mere *conclusory statements*; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.") (emphasis added).

In the present case, the Examiner's reasonable expectation of success appears to rely on (i) the general notion that ***other proteins*** have been successfully biotinylated in and isolated from bacteria, and then properly refolded, and (ii) the alleged statement in Tall *et al.* that LOX-1 (***non-biotinylated***) can be immobilized on a solid surface. However, the general understanding in the recombinant protein art fails to support the notion that ***any*** protein can be expressed in bacteria and properly refolded with a reasonable expectation of success. Further,

the specific understanding in the art with regard to LOX-1 fails to support the premise that ***bacterially-produced*** LOX-1, even assuming that it is properly refolded, would have been reasonably expected to bind its endogenous ligand, as presently claimed.

The general understanding in the recombinant protein art fails to support a reasonable expectation of success. Indeed, as is the case here, persons skilled in the art at the time of invention would ***not*** have reasonably expected to successfully express, isolate, and properly refold a given protein, especially when there is no evidence that said protein has ever been recombinantly produced from ***bacteria***. For example, Swartz (*Curr Opin Biotechnol* 12:195-201, 2001, abstract submitted herewith) teaches that one of the major challenges of producing recombinant proteins in *E. coli* is obtaining the product in a soluble and ***bioactive form***. Likewise, Schendel (*Curr Protoc Mol Biol* Chapter 16:Unit 16.1, 2001, abstract submitted herewith) teaches that despite the years of experience in expressing proteins in bacteria such as *E. coli*, and despite general approaches to solve specific expression problems, ***each new gene still presents its own unique expression problems***, and no single set of methods can guarantee successful production of every protein in a useful form. If each new gene presents its own unique expression problems, then to properly establish a reasonable expectation of success, the cited references must provide some tangible guidance with respect to the bacterial production of a properly folded, extracellular region or CTLD of LOX-1. Since none of the cited references in fact teach the successful expression, isolation, and proper refolding of an extracellular region or a CTLD of LOX-1, let alone ***biotinylated*** LOX-1, the understanding in the recombinant protein art evidences these references fail to provide a reasonable expectation of success in that endeavour.

Moreover, the understanding in the art with regard to LOX-1 fails to support a reasonable expectation of success. As previously made of record, the art clearly teaches that bacterially-produced LOX-1 would ***not*** have been expected to bind with high-affinity to its endogenous ligand, OxLDL. Mainly, it is understood that bacterially-produced LOX-1, as presently claimed, ***inherently*** contains no N-linked high mannose carbohydrate chains, because it was produced in bacteria, such as *E. coli* (*see* Example 2, page 59), that do not have the required glycosylation machinery. Kataoka *et al.* (*Journ. Biol. Chem.* 275:6573-6579, 2000) specifically and explicitly teach the importance of N-linked glycosylation for LOX-1 binding to

OxLDL (*see, e.g.,* Figure 7 of Kataoka *et al.*). According to these clear teachings, persons skilled in the art would not have reasonably expected ***bacterially-produced*** LOX-1 to bind to its endogenous ligand, as presently claimed, and, thus, would not have been motivated to adapt that protein to the instant receptor chip with a reasonable expectation of success.

In this regard, Applicants respectfully disagree with the Examiner's discussion of Kataoka *et al.*, specifically as the teachings of that reference apply to the non-obviousness of the instant claims (*see* the Action, page 8). For one, Applicants are slightly confused by the Examiner's assertion that Kataoka *et al.* focus on SR-PSOX, citing page 40666 of that reference (*see* the Action, page 8). Contrary to this assertion, Kataoka *et al.* focus ***explicitly on LOX-1*** and the role of glycosylation in its ability to efficiently OxLDL. Also, from Applicants' review, this reference neither mentions SR-PSOX, nor does it have a page 40666. Thus, in mis-reading the teachings of Kataoka *et al.*, Applicants can only surmise that the Examiner reviewed the incorrect reference, and submit herewith a new copy of Kataoka *et al.*

Further, it is kindly submitted that the Examiner's stretches the reasonable limits of Tall *et al.* in asserting that it teaches non-glycosylated LOX-1. Indeed, the Examiner further stretches the reasonable limits of Tall *et al.* in asserting that this reference teaches that non-glycosylated LOX-1 is capable of binding OxLDL (*see* the Action, page 8). The Examiner's reading of Tall *et al.* is unreasonable because this reference makes no specific mention of the properties of non-glycosylated LOX-1, but rather discusses the general properties of LOX-1, which is glycosylated in its ***naturally-occurring state***, *i.e.,* its state in a eukaryotic cell (*see* Kataoka *et al.*). Nor do Tall *et al.* provide any data or other specific teachings on the real properties of non-glycosylated LOX-1. Because of this deficiency, the Examiner merely projects the general OxLDL-binding properties of LOX-1 onto the specific properties of bacterially-produced, non-glycosylated LOX-1, without any substantiating evidence, and in direct contradiction to the concrete, experimental data of Kataoka *et al.* Applicants submit that this type of speculative and unsupported assumption cannot support an assertion of obviousness under § 103.

Further, Applicants respectfully submit that the Examiner misses the point in asserting that "since the LOX-1 receptor of Tall *et al.* is also non-glycosylated the protein would

also have the same high binding affinity" (*see* the Action, page 8). Here, the Examiner clearly relies ***impermissibly*** on hindsight, basing her analysis on the unexpected characteristics of bacterially-produced LOX-1, as identified by Applicants' experiments, in which *E. coli*-produced LOX-1 is capable of binding OxLDL. The proper question is whether, given the expectations in the art, a person of ordinary skill in the art would have reasonably expected a bacterially-produced, non-glycosylated LOX-1 to interact with its natural ligand. As previously made of record, and established by concrete, experimental evidence, there is no such reasonable expectation (*see* Kataoka *et al.*). Thus, even assuming, *arguendo*, that the LOX-1 of Tall *et al.* is non-glycosylated in certain instances, as asserted by the Examiner, persons skilled in the art would ***not*** have been motivated to use such a protein in the receptor chip of the instant claims with a reasonable expectation of success, because the experimental evidence of record establishes that non-glycosylated LOX-1 would ***not*** have been expected to bind its natural ligand, as presently claimed.

Overall, Applicants kindly submit that the Examiner's obviousness analysis is inconsistent with the understanding in the recombinant protein arts, the tangible expectations as to LOX-1 specifically, and the caselaw on obviousness. Essentially, the Examiner's asserts that the presently claimed ***compositions*** are obvious merely because, theoretically, there existed an alleged known method of making such compositions, such as by biotinylating LOX-1 in bacteria, and attaching the biotinylated LOX-1 to a chip. However, this analysis ignores the uncertainties with regard to bacterial expression, isolation, and proper refolding of each new protein (*see* Schendel), and would render obvious ***any*** known protein that has been specifically adapted to such methods, regardless of the technical difficulties and uncertainties associated with the same, and the lack of a reasonable expectation of success in that specific endeavour. Because of the tendency to rely on this type of analysis, the courts have stated that for composition claims, as here, "the issue is the obviousness of the claimed compositions, ***not of the method by which they were made***," and that a reasonable expectation of success must be established for the compositions themselves. *See, e.g., In re Bell*, 911 F.2d 718 (Fed. Cir. 1993); and *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991) (emphasis added). Thus, as is the case here, absent tangible, ***technical evidence*** that properly refolded and biotinylated LOX-1 could have been generated

from bacteria with a ***reasonable expectation of success***, and adapted to a receptor chip with the same expectation of success, Applicants submit that it is insufficient to assert that the ***specific*** compositions of the instant claims are obvious merely because of the alleged existence of a ***general*** method of making those types of compositions.

In summary, the cited references contain no technical basis to ***reasonably expect*** that the extracellular region or CTLD of LOX-1, ***specifically***, could have been successfully adapted to the method of Holtzman *et al.*, mainly to produce a (i) ***biotinylated*** and (ii) ***properly folded*** LOX-1 receptor protein. Further, these references contain no technical basis to ***reasonably expect*** that such proteins could have been successfully adapted to a receptor chip, in which the properly folded and biotinylated protein specifically binds its endogenous ligand. By asserting that the claims are obvious, the Examiner makes at least two technical leaps, the ***success*** for which presumably relies on little more than a technically unsupported ***statement*** in Tall *et al.* that LOX-1 (***non-biotinylated***) receptor can be immobilized on a solid surface, and that other proteins have been successfully produced from bacteria. However, given the general expectations in the art with regard to expression and proper refolding of bacterially-produced proteins, and the specific expectations of bacterially-produced LOX-1 (*i.e.,* non-glycosylated) to bind to its endogenous ligand, this line of reasoning is insufficient to establish a reasonable expectation of success. Since a reasonable expectation of success is a required element of a *prima facie* case of obviousness, it is respectfully submitted that the Examiner has not satisfied her burden of proof in establishing that the instant claims are obvious.

As previously made of record, Applicants further submit that the non-obviousness of the instant claims is supported by unexpected results, especially in view of the general understanding in the protein arts, and the specific expectations with respect to bacterially-produced LOX-1 (*see* Kataoka *et al.*). Mainly, Applicants disagree with the Examiner's assertion that Tall *et al.* is at all relevant in this regard (*see* the Action, page 8). Rather, in providing no specific teachings related to non-glycosylated LOX-1, the generalized discussion in Tall *et al.* is too limited to counter the specific expectations created by Kataoka *et al.*, especially because the latter contains real experimental data to support the premise that non-glycosylated LOX-1 would ***not*** have been expected to bind OxLDL. In view of the experimental data of

Kataoka *et al.*, Tall *et al.*'s mere unsupported and generalized references to the ability of LOX-1 to bind its endogenous ligand create no tangible expectations as to specific properties of bacterially-produced, non-glycosylated LOX-1, as presently claimed.

Further, and contrary to the Examiner's assertion (*see* the Action, page 8), the specification need not ***attribute*** the high-binding affinity to the non-glycosylation of LOX-1 to establish unexpected results. Indeed, the instant specification does not ***attribute*** such properties to the non-glycosylation of LOX-1, because the unexpected nature of these results is not necessarily based on glycosylation status being the ***cause*** of high-binding affinity to OxLDL, but is rather based on the observation that bacterially-produced, non-glycosylated LOX-1 binds ***at all*** to OxLDL. In view of Kataoka *et al.*, discussed above, this observation was unexpected. Hence, the non-obviousness of the instant claims is supported by unexpected results; mainly, the binding of bacterially-produced LOX-1 to OxLDL, its endogenous ligand, as presently claimed.

With regard to the rejections outlined in sections B and C above, Applicants also submit that the Examiner has failed to establish a *prima facie* case of obviousness over these claims. *See In re Mayne*, 104 F.3d 1339 (Fed. Cir. 1997) (The USPTO has the burden of showing a *prima facie* case of obviousness). As described above, Holtzman, Schatz and Tall *et al.*, alone or in combination, fail to teach or suggest refolding a biotinylated LOX-1 receptor protein expressed as an ***inclusion body*** within the host. Also, Holtzman, Schatz and Tall *et al.*, alone or in combination, fail to motivate persons skilled in the art to produce a receptor chip comprising an extracellular region or CTLD of LOX-1 protein having the ability to bind its endogenous ligand. Neither Brigham-Burke *et al.* nor Muramatsu remedy these deficiencies, as these references concededly fail to teach a biotinylated LOX-1 protein. Thus, Applicants submit that the present amendments and above remarks also overcome the rejections of dependent claims 17, 44, and 45.

In view of the remarks and amendments provided herein, Applicants submit that claims 1, 17, and 44-45 satisfy the non-obviousness requirement under 35 U.S.C. § 103, and respectfully request withdrawal of this rejection.

Applicants believe that all of the claims in the application are allowable. Favorable consideration and a Notice of Allowance are earnestly solicited.

The Director is authorized to charge any additional fees due by way of this Amendment, or credit any overpayment, to our Deposit Account No. 19-1090.

Respectfully submitted,

SEED Intellectual Property Law Group PLLC

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Enclosures:

Swartz, *Curr Opin Biotechnol* 12:195-201, 2001, abstract.
Schendel, *Curr Protoc Mol Biol* Chapter 16:Unit 16.1, 2001, abstract.
Kataoka *et al.*, *Journ. Biol. Chem* 275:6573-6579, 2000.

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